Ann Natl Acad Med Sci (India), **46(2):** 87-97, 2010

Evidence-based Interventions to Prevent Vascular Complications in Diabetes Mellitus

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Abstract

Vascular disease afflicts diabetics more frequently than non diabetics. Microvascular disease is almost exclusively a problem of patients with diabetes mellitus. During the later half of the 20th century there have been several clinical trials which have tried to study the impact of glycemic control on prevention/progression of vascular disease in patients with diabetes mellitus. Some of these are reviewed here.

Evidence-based Interventions to Prevent Vascular Complications in Diabetes Mellitus

Diabetes mellitus was recognized by Indian physicians more than 2000 years ago. It is a complex metabolic disorder associated with derangement in carbohydrate, protein and lipid metabolism. Discovery and availability of insulin during the early part of 20th century lead to significant improvement in the quality and quantity of life for diabetics. Introduction of oral hypoglycemic drugs in the 1950s provided an alternative to the discomfort and stigma of injections for patients with type 2 diabetes. As the therapeutic options increased clinical trials, to assess the safety and efficacy of different therapeutic agents and the impact of therapy on different diabetes-associated problems, started during the later part of 20th century. This article is a review of some of these mega trials.

UGDP Study

Vascular disease afflicts diabetics more frequently than non diabetics. UGDP was designed to find out if blood glucose control helps to prevent or delay vascular disease in diabetics who did not require insulin to prevent acute ketoacidosis (1-5). Study was planned in

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1959-60. It started as 4 treatment groups, tolbutamide, insulin standard dose, insulin variable dose and placebo. Later another group DBI-TD (phenformin) was added to the study in 1962. All patients received the same diet prescription in terms of percentage of carbohydrate, protein and fat. The insulin variable group was given as much insulin as required to maintain normal blood glucose (fasting <100 mg/dl and 1 hour post 50 gm glucose and 1½ hours after insulin <150 mg/dl). Insulin standard dose received 10, 12, 14 or 16 units insulin per day depending on body surface area. Tolbutamide group received 1.5 gm (1 gm before breakfast and 0.5 gm before evening meal) daily. Phenformin group received 100 mg daily. A total of 1027 patients were enrolled in 12 study centers. Patients were eligible to enter this study if the duration of diabetes was less than 1 year. Patients were randomized into any one of these study groups and were followed up with quaterly examination for a 10-year period (Tables 1, 2 and 3).

Table 1: Sequence of UGDP events by calendar year

Year	Event
1959	Planning phase began.
1960	Objectives formulated and first version of protocol written. NIAMD awards granted to first five clinics. Forms and manual of operations developed. Manufacturers of drugs and urine test reagents agreed to supply with their products.
1961	Patient recruitment began. Two additional clinics joined study. Study protocol finalized.
1962	Phenformin was added to study. Three additional clinics joined study.
1963	Last two clinics entered study.
1966	Recruitment of patients completed. Extensive six-year progress report prepared.
1967	NIAMD grant support renewed for five years.
1969	Tolbutamide treatment discontinued.
1970	Papers prepared on *Design, Methods and Baseline Results* and on *Mortality Results.*

Table 2: Study Treatments

Treatment	Abbreviation	Dosage
Insulin Variable (U-80 Lente Iletin or other insulins	IVAR	As much insulin as is required to maintain "normal" blood glucose. The minimum dose is five units per day.
Insulin Standard (U-80 Lente Iletin insulin)	ISTD	10, 12, 14 or 16 units per day depending on the patient's body surface.
Tolbutamide (Orinase)	TOLB	1.5 gm per day (1 gm before breakfast and 0.5 gm before the evening meal)
Phenformin (DBI-TD)	PHEN	100 mg per day: 50 mg before breakfast and 50 mg before the evening meal. First week of study only 50 mg before breakfast.
Lactose Placebo	PLBO	Dosage schedules corresponding to those used for oral hypoglycemic agents.

Table 3: Percentage distribution of patients by age and sex at entry

Age at Entry	Male	Female	All Patients
20-24	0.3	0.8	0.7
25-29	1.4	2.2	1.9
30-34	1.4	3.0	2.5
35-39	6.1	8.2	7.6
40-44	10.2	13.4	12.5
45-49	14.0	12.3	12.8
50-54	15.3	16.0	15.8
55-59	19.0	15.4	16.5
60-64	14.6	14.6	14.6
65-59	10.9	9.3	9.7
70-74	6.1	3.3	4.1
75-79	0.7	1.6	1.4
No. of patients	**294**	**733**	**1,027**

Mean starting fasting blood glucose was 140 mg/dl. Blood glucose decreased from 13% to 24% in different treatment groups during the first follow up visit, but gradually increased in all groups except in insulin variable group. Nearly 10% of patients had dose adjustment for presumed hypoglycemia. Only 12 patients had recorded fasting glucose (during follow up visits) <50 mg/dl.

In October 1969 a total of 89 deaths were reported in the initial 4 groups (table 4). Among them 10% were on placebo, 15% tolbutamide, 10% in insulin standard and 9% among insulin variable. Deaths from cardiovascular causes were 5% for placebo, 13% for tolbutamide, 6% for ISTD and 6% for insulin variable group. Cancer deaths were more among the placebo group.

UGDP investigators agreed that the findings of this study indicated that the combination of tolbutamide and diet was less effective than diet alone or other treatment groups as far as cardiovascular mortality was concerned. Therefore, use

Table 4: Number and percent dead by cause of death

	PLBO	TOLB	ISTD	IVAR
Number at Risk of Death	205	204	210	204
CARDIOVASCULAR CAUSES				
1. Myocardial Infarction	0	10	3	2
2. Sudden Death	4	4	4	5
3. Other Heart Disease	1	5	1	2
4. Extracardiac Vascular Disease	5	7	5	3
All C.V. Causes	10	26	13	12
NONCARDIOVASCULAR CAUSES				
5. Cancer	7	2	4	2
6. Cause Other Than 1-5	3	2	2	3
7. Unknown Cause	1	0	1	1
All causes	21	30	20	18
Per cent Dead From :				
C.V. Causes	4.9	12.7	6.2	5.9
All Causes	10.2	14.7	9.5	8.8

of tolbutamide was discontinued. Insulin variable was more effective than all other treatment groups in maintaining fasting blood glucose. Mortality was comparable to placebo group. Recent studies have shown that sulphonylurea block ischemic pre conditioning of heart (a protective mechanism to reduce ischemic damage). This possibly explains the excess CV deaths in this study (5).

Phenformin group

Effect of phenformin therapy was based on the results of 401 patients assigned to placebo (64), insulin (133) or phenformin (204) in 6 clinics (6). Number of deaths in these three groups were 7, 10 and 34 for placebo, insulin and phenformin respectively. Mortality from all causes and from cardiovascular causes were higher for phenformin treated group compared to any other treatment group. Also, phenformin therapy resulted in increased blood pressure and heart rate. These observations gave no evidence to suggest that phenformin was more effective than diet alone or in combination with insulin in prolonging life as used in UGDP. Therefore, use of this drug was discontinued.

UKPDS

The UK Prospective Diabetes Study, which started in 1977, was designed to test if intensive blood glucose control in patients with type 2 diabetes mellitus reduced micro or macro vascular complications and whether any particular therapy was advantageous (7). 3867 newly diagnosed type 2 diabetes mellitus patients (who had a mean of 2 fasting glucose values between 6.1 and 15 mmol/L after 3 months of diet therapy) were randomly assigned to conventional or intensive therapy.

The aim of conventional therapy was to maintain fasting blood glucose below 15 mmol/L without symptoms of hyperglycemia. The aim of intensive treatment was fasting plasma glucose less than 6 mmol/L and in insulin treated group, pre meal glucose of 4-7 mmol/L. The doses of sulphonylurea used were chlorpropamide 100-500 mg, glibenclamide 2.5 to 20 mg and glipizide 2.5 to 4 mg. Whenever glucose concentration was above target level dose adjustment was done. Patient assigned insulin therapy was started on once daily ultra lente or isophane insulin. If dose requirement was more than 14 units or pre meal or bed time glucose was more than 7 mmol/L a short acting insulin was added. All patients received dietary advice from a dietician. Median age of patients was 54 years. Over 10 years HbA1c was 7% in the intensive group compared to 7.9% in the

conventional group (11% reduction). There was no difference between different therapeutic agents. There was a 25% reduction in micro-vascular end points in the intensive group (no difference in sub groups). Patients in the intensive group had more hypoglycemic events and weight gain (most in insulin treated group). They concluded that intensive blood glucose control by either sulphonylureas or insulin substantially decreases the risk of microvascular (non macrovascular) complications in patients with type 2 diabetes mellitus. None of the individual drugs had an adverse effect on cardiovascular outcomes. All intensive treatment increased risk of hypoglycemia.

Effect of metformin (UKPDS)

1704 of the 4075 patients recruited to UKPDS with newly diagnosed type 2 diabetes were overweight (>120 ideal body weight) and had raised fasting blood glucose (6.1 to 15 mmol/L) without hyperglycemic symptoms after 3 months of initial diet therapy. These patients were randomized into 3 arms, diet (conventional treatment, 411 subjects) intensive control with metformin (342 subjects), intensive control with sulphonylurea or insulin (951 subjects) (8). In a supplementary study 537 non overweight and overweight patients, mean age 55 years who were already on maximum sulphonylurea therapy but had raised fasting blood glucose (6.1-15 mmol/L) were randomly allocated to SU therapy alone (269) or addition of metformin (268).

There was reduction in HbA1C (median 8 to 7.4) and diabetes related end points (42% reduction for diabetes related death and 36% all cause mortality) compared to the conventional group. Metformin showed a greater effect among the intensively treated compared to sulphonylurea and insulin. However, addition of metformin to sulphonylurea was associated with an increased risk of diabetes related death compared to sulphonylurea alone. This study concluded that since intensive treatment with metformin reduced risk of diabetes related endpoints in overweight diabetic patients and was associated with less weight gain and hypoglycemic episodes than insulin and SUs, it may be the first line pharmacological therapy of choice in these patients.

10 year follow up

Post trial monitoring was done to determine whether improved glucose control persisted and whether such therapy had a long term effect on macro

vascular complications (9). Patients were asked to attend annual UKPDS clinics for 5 years, but no attempt was made to maintain their previously assigned therapies. From 6th to 10th year patients were assessed through questionnaires.

Between group differences in glycosylated haemoglobin levels were lost after first year. Despite this loss of difference, there was continued reduction in microvascular risk and emergent risk reductions for myocardial infarction and death from any cause. Continued benefit of metformin therapy was observed for overweight patients. However, the benefits of previously improved blood pressure control were not sustained when the between group blood pressure differences were lost. This study has documented benefits of blood glucose and blood pressure control on micro- and macrovascular diseases and also the existence of metabolic memory for glucose and lack of metabolic memory for blood pressure.

Diabetes Control and Complications Trial (DCCT) was a multi center randomized clinical trial which was designed to compare intensive with conventional diabetes therapy to assess its effect on development and progression of early vascular and neurological complications of insulin-dependent diabetes mellitus (IDDM, now called Type 1 DM) (10). Intensive therapy aimed at controlling blood glucose levels as close to normal as possible with multiple injections or an insulin pump. Two cohorts of patients were studied: one with no retinopathy (primary prevention) and the other with early retinopathy (secondary prevention).

1441 patients with IDDM (726 without retinopathy and 715 with mild retinopathy) were included in this study. They were randomly assigned to intensive or conventional therapy and followed up for a mean of 6.5 years. Appearance and progression of retinopathy and other complications were regularly assessed.

Glycosylated haemoglobin was reviewed at 6 months in the intensive therapy group. About 44% of patients in the intensive group achieved HbA1C value of 6.05% or less at least once during the study period; less than 5% maintained a value in this range during the study period. Mean blood glucose value of intensive group was 155 ± 30 mg/dl vs 231 ± 55 mg/dl in the conventional group. There was a 76% reduction in the development of retinopathy (primary prevention) and 54% reduction in progression of retinopathy (secondary prevention).

Intensive therapy reduced albuminuria by 54%, microalbuminuria by 39% and neuropathy by 60%. But this was associated with a 2 to 3 fold increase in severe hypoglycemia. This study concluded that intensive therapy delays the onset and slows the progression of diabetic retinopathy, nephropathy and neuropathy in patients with insulin dependent diabetes mellitus.

The DCCT demonstrated that maintaining HbA1c levels as close to normal as feasible reduced the risks for development and progression of early microvascular and neurological complications of type I diabetes. While reductions of early stages of diabetic complications could reasonably be expected to slow the evolution to end stage disease (visual loss, renal failure), few such complications occurred during DCCT to establish that conclusion. Similarly, although fewer intensively treated diabetics experienced cardiovascular events the numbers were too small to be conclusive. Epidemiological studies suggest that overt late stage complications usually occur after 15 – 25 years duration of type I diabetes. The DCCT Cohort had an average duration of diabetes of 12 years at study end.

All the participants of DCCT were advised to follow intensive therapy and subsequently followed up in an observational study (EDIC) (11). Out of 1425 living members of the original Cohort 1388 participated in the EDIC study. Epidemiology of Diabetes Interventions and Complications (EDIC) study followed up subjects who took part in the DCCT study 1983-93, till 2005. This was an observational study to assess cardiovascular disease (non fatal myocardial infarction, stroke, CVD). During a mean follow up of 17 years there were 46 CVD events in 31 patients in the intensive group compared to 98 events in 52 patients in the conventional group. They concluded that intensive therapy has long term beneficial effects on the risk of CVD in type 1 diabetics. In addition to benefits on complication this study also showed benefits on beta cell preservation and decreased incidence of hypertension among the intensively treated group.

Kumomoto study is an 8 year randomized prospective study of Japanese patients with type 2 diabetes mellitus (12). They tested if intensive glycemic control decreased the severity or frequency of diabetic microvascular complications. One hundred and ten patients with type 2 diabetes (55 with no retinopathy- primary intervention cohort

and 55 with simple retinopathy-secondary intervention cohort) were randomly assigned to conventional insulin therapy (CIT) or multiple injection insulin therapy (MIT). Conventional group received one or two doses of intermediate acting insulin while the MIT group received short acting insulin at each meal and intermediate acting insulin at bedtime. The goal of conventional group was to have no symptoms of hypo or hyperglycemia and fasting glucose <140 mg/dl. The goal of MIT group was fasting glucose <140 mg/dl, 2 hour post meal glucose <200mg/dl and HbA1c <7%. In both primary and secondary intervention groups the cumulative incidence of retinopathy and nephropathy were less in the MIT group. They estimated the glycemic threshold for prevention or progression of microvascular complication as HbA1c <6.5%, fasting glucose <110 mg/dl and 2 hour post meal glucose <180 mg/dl.

Three large studies published recently (ACCORD, ADVANCE, VADT) have shown inconsistent results regarding effects of glycemic control on macrovascular disease (13). This has raised issues of individualization of glycemic targets based on age of patient, duration of diabetes, presence of other co-morbid conditions and nature of drugs used.

Salient facts emerging from these studies merit recall. The UGDP study enrolled newly diagnosed type 2 diabetics. The results of this study generated a lot of debate starting from the design of study, choice and dose of therapeutic agents and the statistical analysis. Use of phenformin nearly came to an end after this (3-5). The UKPDS, DCCT and Kumomoto study showed intensive therapy decreased HbA1c and lowering of HbA1c lead to prevention/ prevention of progression of microvascular complications and some reduction in macrovascular complications. The benefits of blood glucose control persisted even after differences in HbA1c disappeared (metabolic memory). HbA1c lowering with intensive therapy was associated with two to three fold increase in hypoglycemic events. The Kumomoto study, possibly more relevant for Indian population, showed that multiple doses with short acting insulin, without increasing total dose, could achieve lower HbA1c. They suggested cut offs of 6.5% for HbA1c, 110 mg/dl for fasting glucose and 180 mg/dl post meal glucose for prevention of vascular complications. Recent studies (13) which assessed effect

of tight blood glucose control on cardiovascular health observed inconsistent results.

These studies have confirmed what has been generally observed in clinical practice i.e. treatment needs to be individualized. While it is possible to achieve normoglycmia in newly diagnosed diabetics with small doses of insulin or OHA (14), the same is not possible in those with long standing diabetes/diabetics with other co-morbidities. Treatment targets should be carefully chosen taking into consideration the age of the individual, duration of diabetes, other medical co-morbidities, patient need and socio economic factors. The most important person in this whole exercise is the patient. Therefore, extensive patient education is required to overcome barriers to optimal therapy.

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